The hetero Diels–Alder reactions of masked *o*-benzoquinones with nitroso compounds

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The first examples of hetero Diels–Alder reaction of masked *o*-benzoquinones with nitroso dienophiles leading to novel and highly functionalized heterocycles, which are potential intermediates for nitrogenous natural products are reported.

The hetero Diels–Alder reaction represents a powerful strategy for the stereoselective construction of highly functionalized heterocyclic systems.[1] A nitroso function that is directly linked with an electron-withdrawing group acts as an efficient dienophile as a result of extremely low LUMO energy and weak π-bond.[2] Acyl nitroso compounds have been used as dienophiles in both intermolecular and intramolecular versions of hetero Diels–Alder reactions to produce highly functionalized cycloadducts that provide valuable synthetic intermediates to a variety of biologically interesting molecules.[1,3]

Masked *o*-benzoquinones (MOBs),[4] a highly reactive class of 2,4-cyclohexadienones with extensive utility can be generated by the oxidation of easily available 2-methoxyphenols using hypervalent iodine reagents such as diacetoxyiodobenzene (DAIB) and phenyliodonium(III) bis(trifluoroacetate) (PIFA) in MeOH. In the course of our investigations on MOB chemistry, we have developed methods for their *in situ* generation and studied their inter-[5] and intramolecular[6] carbo-Diels–Alder reactions. The synthetic potential of this methodology has been demonstrated in the total/formal syntheses of several natural products by us[7] and others.[8] Very recently, MOBs were shown to drive heteroaromatics such as furans,[9] pyrroles[10] and indoles[11] as 2π-components in the carbo-Diels–Alder reaction. In continuation of our efforts to broaden the versatility of MOBs, we contemplated their hetero Diels–Alder reaction with nitroso dienophiles to generate functionalized bicyclo[2.2.2]octenone derivatives that are possible intermediates for several biologically active natural products such as aminocyclitols,[12] pancratistatin[13] and tetrodotoxin[14] (Scheme 1).

Owing to their highly reactive nature, both MOB (diene) and nitroso dienophile were transiently generated in the reaction medium. Thus, at the outset of our study, we examined the reaction of MOB **1a**, obtained from the parent 2-methoxyphenol *i.e.* guaiacol (**2a**), with nitroso compound **3a**. The oxidation of **2a** with DAIB in MeOH produced MOB **1a** and the periodate oxidation of *tert*-butyl *N*-hydroxycarbamate (**4a**) produced **3a**. When the reaction was performed with an equimolar ratio of **2a** and **4a**, the two transient intermediates reacted very efficiently at 0 °C to furnish the Diels–Alder adduct **5a** in 80% yield. However, use of two equivalents of **4a** under the same

conditions increased the yield to 90%. This overwhelming result prompted us to extend this reaction to other 2-methoxy-phenols. Thus, a variety of phenols **2b–j** in the reaction with **4a** were examined as summarized in Scheme 2 and Table 1.† The MOBs **1b–g** reacted very smoothly with nitroso compound **3a** at 0 °C resulting in the formation of adducts **5b–g** in good to excellent yields (entries 1, 3, 5, 7, 9, 11 and 13). However, the reactions of phenols **2h–j** bearing electron-releasing substituents at C-4 did not proceed at 0 °C. A workable solution was found by the slow addition of hydroxamic acid **4a** to a mixture of phenol **2h** and oxidants in MeOH–CH₂Cl₂ at 50 °C and continuing the reaction at the same temperature. Under these

for **3a**, **4a**, **5a-j**: R = Boc
for **3b**, **4b**, **6a-j**: R = Cbz
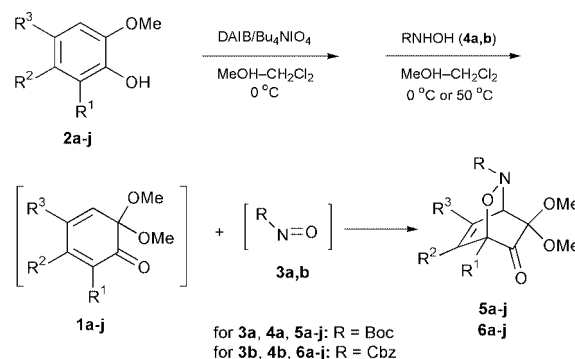
Scheme 2

Table 1 Hetero Diels–Alder reaction of masked *o*-benzoquinones **1a–j** with BocNO (**3a**) and CbzNO (**3b**)

Entry	MOB			Nitroso compd	Temp.[a]/ °C	Time[b]/ h	Adduct (Yield (%))[c]
	R¹	R²	R²				
1	**1a** H	H	H	**3a**	0	1	**5a** (90)
2				**3b**	0	1	**6a** (96)
3	**1b** H	CO₂Me	H	**3a**	0	1	**5b** (71)
4				**3b**	0	1	**6b** (81)
5	**1c** H	Me	H	**3a**	0	1	**5c** (93)
6				**3b**	0	1	**6c** (95)
7	**1d** H	(dioxolane)	H	**3a**	0	1	**5d** (92)
8				**3b**	0	1	**6d** (96)
9	**1e** Me	H	H	**3a**	0	1	**5e** (69)
10				**3b**	0	1	**6e** (81)
11	**1f** H	H	CO₂Me	**3a**	0	1	**5f** (70)
12				**3b**	0	1	**6f** (74)
13	**1g** H	H	COMe	**3a**	0	1	**5g** (57)
14				**3b**	0	1	**6g** (52)
15	**1h** H	H	Me	**3a**	50	3	**5h** (84)
16				**3b**	50	3	**6h** (90)
17	**1i** H	H	(dioxane)	**3a**	50	12	**5i** (71)
18				**3b**	50	12	**6i** (92)
19	**1j** H	H	Br	**3a**	50	12	**5j** (91)
20				**3b**	50	12	**6j** (90)

[a] Reaction temperature. [b] Reaction time after the addition of RNHOH. [c] Yields of pure and isolated adducts.

Scheme 1

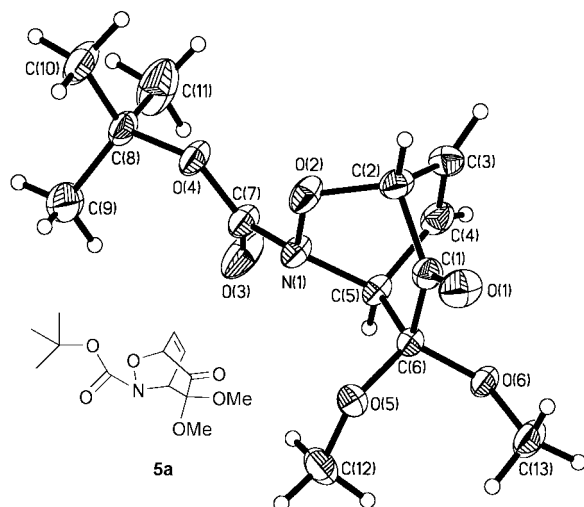Aminocyclitols   Pancratistatin   Tetrodotoxin

DOI: 10.1039/b103649c
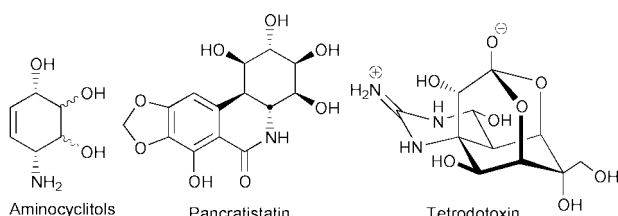
Fig. 1 ORTEP plot of the crystal structure of cycloadduct **5a** (numbering is arbitrary).

conditions, phenols **2h**–**j** afforded the cycloadducts **5h**–**j** in high to excellent yields (entries 15, 17 and 19).

In an effort to ascertain whether the *N*-substitution of nitroso compound has influenced the reaction, we have evaluated the Diels–Alder reaction of MOBs **1a**–**j** with (*N*-carbobenzyloxy)nitroso compound **3b** (Scheme 2). These cycloadditions were found to be quite efficient and the adducts **6a**–**j** were obtained in very good to excellent yields. These results are summarized in Table 1.

The structures of all the cycloadducts were based on the IR, [1]H (400 MHz) and ^{13}C (100 MHz) NMR, DEPT, low-, and high-resolution mass spectral analyses. The regiochemistry of the adduct **5a** was confirmed by its single crystal X-ray structure (Fig. 1)‡ and that of the adducts **5b**–**j** and **6a**–**j** is derived by comparing the chemical shifts of their ^{1}H NMR spectra with that of **5a**.

The excellent regioselectivity of this Diels–Alder reaction is in full agreement with our earlier studies on Diels–Alder reactions of MOBs.[5,9–11] The moderately stable MOBs such as **1i,j** require higher temperature and prolonged reaction times for the reaction as reflected by the reaction conditions employed for phenols **2i,j** (entries 17–20), which is in accordance with our earlier findings.[15]

In conclusion, bicyclo[2.2.2]octenone derivatives embedded with heteroatoms—types of substrate that are useful in the total syntheses of natural products possessing an aminopolyhydroxycyclohexane or cyclohexene moiety—are accessed in a highly regioselective manner from simple 2-methoxyphenols. The simplicity of the experimental procedure and the ready accessibility of masked *o*-benzoquinones and nitroso dienophiles thus renders this an experimentally attractive method for the preparation of nitrogenous heterocycles. Currently, we are actively pursuing the transformation of such cycloadducts to pertinent targets including conduramines and natural products such as pancratistatin and tetrodotoxin.

Notes and references

† *General procedure for phenols* **2a**–**g** *and* N-*hydroxycarbamates* **4a,b**: to a stirred mixture of DAIB (1.1 mmol) and Bu$_4$NIO$_4$ (2 mmol) in MeOH (5 mL) at 0 °C, was added phenol **2** (1 mmol) in CH$_2$Cl$_2$ (5 mL) at once. After 10 min of stirring at 0 °C, was added carbamate **4** (2 mmol) in a 1 : 1 mixture of MeOH–CH$_2$Cl$_2$ (5 mL) at once and the reaction was continued for 1 h at the same temperature. Then the solvent and other volatiles were removed under reduced pressure and the residue was subjected to silica gel column chromatography (ethyl acetate–hexanes) to obtain pure cycloadducts **5a**–**g** and **6a**–**g**.

General procedure for phenols **2h**–**j** *and* N-*hydroxycarbamates* **4a,b**: To a stirred mixture of DAIB (1.1 mmol) and Bu$_4$NIO$_4$ (2 mmol) in MeOH (5 mL) at 0 °C, was added phenol **2** (1 mmol) in CH$_2$Cl$_2$ (5 mL) at once. After 10 min of stirring at 0 °C, the reaction flask was moved to a preheated oil bath (50 °C), and carbamate **4** (2 mmol) in a 1 : 1 mixture of MeOH–CH$_2$Cl$_2$ (5 mL) was added dropwise using a syringe pump (addition time: 1 h for entries 15 and 16, 4 h for entries 17 and 18, and 8 h for entries 19 and 20) and the reaction was continued [for 3 h (entries 15 and 16) or 12 h (entries 17–20)] at the same temperature. Thus formed adducts **5h**–**j** and **6h**–**j** were isolated as described in the above procedure.

‡ *Crystal data* for **5a**: C$_{13}$H$_{19}$NO$_6$, M = 285.29, triclinic, a = 12.035(2), b = 6.288(2), c = 19.541(2) Å, α = 90, β = 100.71(2), γ = 90°, V = 1453.0(6) Å^3, T = 295(2)K, space group $P2_1$, Z = 4, μ(Mo-Kα) = 0.103 mm^{-1}, 3344 reflections collected, independent reflections (R_{int} = 0.0000), final R indices [$I > 2\sigma(I)$], $R1$ = 0.0418, $wR2$ = 0.1249. CCDC 161113. See http://www.rsc.org/suppdata/cc/b1/b103649c/ for crystallographic data in CIF or other electronic format.

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